Claims

1. A method of increasing angiogenesis in a mammal by providing to said mammal a therapeutically effective amount of Related Transcriptional Enhancer Factor-1 (RTEF-1) polypeptide, wherein said RTEF-1 has angiogenic activity and at least 60% sequence identity to the sequence of human RTEF-1 (Accession Number AAC50763), mouse RTEF-1 (Accession Number Q62296), or chick RTEF-1 (Accession Number P48984).

2. The method of claim 1 further comprising providing a therapeutically effective amount of Hypoxia-Inducible Factor (HIF)-1α to said mammal.

3. A method of increasing angiogenesis in a mammal by providing to said mammal a nucleic acid molecule encoding Related Transcriptional Enhancer Factor-1 (RTEF-1) in a therapeutically effective amount, wherein said RTEF-1 has angiogenic activity and at least 80% sequence identity to the sequence of human RTEF-1 (Accession Number AAC50763), mouse RTEF-1 (Accession Number Q62296), or chick RTEF-1 (Accession Number P48984).

4. The method of claim 3 further comprising providing a nucleic acid encoding Hypoxia-Inducible Factor (HIF)-1α in a therapeutically effective amount to said mammal.

5. The method of claim 1 or 3, wherein said RTEF-1 is provided into cells within or adjacent to an ischemic tissue.

6. A method of increasing angiogenesis in a mammal by providing to said mammal a cell, tissue, or organ that contains Related Transcriptional Enhancer Factor-1 (RTEF-1) in a therapeutically effective amount, wherein said RTEF-1 has angiogenic activity and at least 80% sequence identity to the sequence of human RTEF-1 (Accession Number AAC50763), mouse RTEF-1 (Accession Number Q62296), or chick RTEF-1 (Accession Number P48984).

7. The method of claim 6, wherein cell, tissue, or organ further contains Hypoxia-Inducible Factor (HIF)-1α in a therapeutically effective amount.

8. The method of claim 6, wherein said cell or said tissue is provided to said mammal within or adjacent to an ischemic tissue.

9. The method of claim 6, wherein said cell, tissue, or organ has at least 10% or more RTEF-1 polypeptide present, relative to a control cell, tissue, or organ.

10. The method of claim 6, wherein said cell, tissue, or organ has been provided with an RTEF-1 polypeptide or a nucleic acid molecule encoding RTEF-1.

11. The method of claim 6, wherein said providing is *ex vivo*.

12. The method of claim 6, wherein said cell, tissue, or organ is from an autologous source.

13. The method of claim 6, wherein said cell, tissue, or organ is from an allogeneic donor mammal.

14. The method of claim 6, wherein said cell is a myocyte, fibroblast, myoblast, endothelial cell, cardiomyocyte, cardioblast, or smooth muscle cell.

15. The method of claim 14, wherein said cell is an endothelial cell.

16. The method of claim 6, wherein said cell, tissue, or organ is, or is from, a heart, liver, muscle, lung, pancreas, brain, skin, kidney, or eye.

17. The method of claim 3 or 10, wherein said nucleic acid molecule is an expression vector selected from the group consisting of a plasmid or a viral vector.

18. The method of claim 17, wherein said viral vector is selected from the group consisting of an adenovirus, retrovirus, adeno-associated virus vector, herpes simplex virus, SV40 vector, polyoma virus vector, papilloma virus vector, picarnovirus vector, and vaccinia virus vector.

19. The method of claim 3 or 10, wherein said RTEF-1 is under the control of a tissue-specific promoter.

20. The method of claim 18, wherein said promoter is specific to endothelial cells, cardiomyocytes, skin cells, hepatocytes, myocytes, adipocytes, fibroblasts, or the tissue or cell type in which the RTEF-1 is to be provided.

21. The method of claim 1, 3, or 6, wherein said mammal is diagnosed as having an ischemic condition.

22. The method of claim 21, wherein said ischemic condition is selected from the group consisting of cardiac infarction, chronic coronary ischemia, chronic lower limb ischemia, stroke, cerebral ischemia, and peripheral vascular disease.

23. The method of claim 22, wherein said mammal is diagnosed as having myocardial ischemia.

24. The method of claim 1, 3, or 6, wherein said mammal is diagnosed as having a myocardial infarct, unstable angina, cardiac hypertrophy, arrhythmia, cardiomyopathy, angina pectoris, atherosclerosis, arteriosclerosis, a complication of diabetes, restenosis, organ hypertrophy, organ hyperplasia, septic shock, inflammatory disease, or myocardial dysfunction.

25. The method of claim 1, 3, or 6, wherein said providing is within three days before or after said mammal has a trauma or surgical procedure, or experiences physical trauma.

26. The method of claim 25, wherein said surgical procedure is selected from the group consisting of coronary bypass surgery, vascular surgery, percutaneous transluminal coronary angioplasty, percutaneous transluminal coronary intervention, and organ transplantation.

27. The method of claim 1, 3, or 6, wherein said RTEF-1 increases VEGF, FGFR, or COX-2 levels in the target tissue of said mammal by at least 20% relative to an untreated control.

28. The method of claim 27, wherein said RTEF-1 increases VEGF, FGFR, or COX-2 levels in the target tissue of said mammal by at least 40% relative to an untreated control.

29. The method of claim 1, 3, or 6, wherein said RTEF-1 increases collateral blood vessel formation, improves abnormal cardiac function, or increases contractility of heart muscle.

30. The method of claim 1, 3, or 6, wherein said mammal is further provided with a second therapeutic regimen.

31. The method of claim 30, wherein said second therapeutic regimen is a therapeutic agent selected from the group consisting of nitrates, beta-blockers, calcium channel blockers, aspirin, nitroglycerin, chelation therapy, ethylenediaminetetracetic acid, anticoagulants, thrombolytic drugs, and tissue plasminogen activators.

32. The method of claim 30, wherein said second therapeutic regimen is surgery.

33. The method of claim 32, wherein said surgery is selected from the group consisting of coronary bypass surgery, vascular surgery, percutaneous transluminal coronary angioplasty, percutaneous transluminal coronary intervention, and organ transplantation.

34. The method of claim 30, wherein said second therapeutic regimen is exercise, reduction in smoking, reduction in alcohol intake, low sodium diet, low fat diet, low cholesterol diet, or stress management.

35. The method of claim 30, wherein said RTEF-1 and said second therapeutic agent are provided within ten hours of each other.

36. The method of claim 30, wherein said RTEF-1 and said second therapeutic agent are provided simultaneously or within one hour of each other.

37. The method of claim 30, wherein said RTEF-1 and said second therapeutic agent are administered in the same pharmaceutical formulation.

38. A method of decreasing angiogenesis in a mammal by administering to said mammal a therapeutically effective amount of a composition that reduces the expression or activity of Related Transcriptional Enhancer Factor-1 (RTEF-1).

39. The method of claim 38 further comprising administering a therapeutically effective amount of a composition that reduces the expression or activity of Hypoxia-Inducible Factor (HIF)-1α.

40. The method of claim 38, wherein said composition decreases VEGF, FGFR, or COX-2 levels in the target tissue of said mammal by at least 20% relative to an untreated control.

41. The method of claim 40, wherein said RTEF-1 decreases VEGF, FGFR, or COX-2 levels in the target tissue of said mammal by at least 40% relative to an untreated control.

42. The method of claim 38, wherein said composition is selected from a peptide, a polypeptide, a synthetic organic molecule, a naturally occurring organic molecule, a nucleic acid molecule, an antibody, or an antigen binding fragment.

43. The method of claim 42, wherein said nucleic acid molecule is an antisense RNA molecule that is complementary to at least a portion of RTEF-1 sense nucleic acid sequence or is a double-stranded RNA (dsRNA) molecule that comprises a portion of RTEF-1 nucleic acid sequence and that is cleaved in a cell of said mammal to produce a short interfering RNA (siRNA) molecule, and wherein said nucleic acid molecule is sufficient to cause a decrease in RTEF-1 biological activity in said mammal.

44. The method of claim 38, wherein said mammal is diagnosed with cancer, acquired immune deficiency syndrome (AIDS), diabetes, arthritis, psoriasis, or ocular disease.

45. The method of claim 44, wherein said ocular disease is macular degeneration or diabetic retinopathy.

46. The method of claim 44, wherein said cancer is selected from the group consisting of breast cancer, prostate cancer, brain cancer, pancreatic cancer, lung cancer, stomach cancer, ovarian cancer, cervical cancer, leukemia, lymphoma, and AIDS-related Kaposi's sarcoma.

47. The method of claim 38, wherein said mammal is further provided with a second therapeutic regimen.

48. The method of claim 47, wherein said second therapeutic regimen is selected from the group consisting of chemotherapy, radiotherapy, hormone ablation therapy, anti-inflammatory agents, and steroids.

49. The method of claim 47, wherein said composition and said second therapeutic regimen are provided within ten hours of each other.

50. The method of claim 47, wherein said composition and said second therapeutic regimen are provided simultaneously or within one hour.

51. The method of claim 47, wherein said second therapeutic regimen is a therapeutic agent and said composition and said second therapeutic agent are administered in the same pharmaceutical formulation.

52. The method of any one of claims 1, 3, 6, or 38, wherein said mammal is a human.

53. The method of any one of claims 1, 3, or 6, wherein said RTEF-1 has at least 85 % sequence identity to the sequence of human RTEF-1 (Accession Number AAC50763), mouse RTEF-1 (Accession Number Q62296), or chick RTEF-1 (Accession Number P48984).

54. A method for identifying a candidate compound for increasing angiogenesis in a mammal, said method comprising:

(a) contacting a sample comprising Related Transcriptional Enhancer Factor-1 (RTEF-1) gene with a candidate compound; and

(b) measuring RTEF-1 gene expression or activity, wherein a candidate compound that alters RTEF-1 gene expression or activity, relative to RTEF-1 expression or activity in a sample not contacted with said candidate compound, is a candidate compound that may be useful for modulating angiogenesis in a mammal.

55. The method of claim 54, wherein said sample comprises a cell expressing RTEF-1 and said measuring step (b) comprises measuring RTEF-1 gene expression or activity in said cell.

56. A method for identifying a candidate compound for decreasing angiogenesis in a mammal, said method comprising:

(a) contacting a sample comprising a Related Transcriptional Enhancer Factor-1 (RTEF-1) gene with a candidate compound; and

(b) measuring said RTEF-1 gene expression or activity in said sample, wherein a candidate compound that alters said RTEF-1 gene expression or activity, relative to RTEF-1 expression or activity in a sample not contacted with said

candidate compound, is a candidate compound that is useful for modulating angiogenesis in a mammal.

57. The method of claim 56, wherein said sample comprises a cell expressing RTEF-1 and said measuring step (b) comprises measuring RTEF-1 gene levels or activity in said cell.

58. The method of claim 54 or 56, wherein step (b) comprises measuring levels of RTEF-1 mRNA or polypeptide.

59. The method of claim 54 or 56, wherein said RTEF-1 gene is a RTEF-1 fusion gene.

60. The method of claim 54 or 56, wherein said cell is a mammalian cell.

61. The method of claim 60, wherein said cell is a rodent cell.

62. A method for identifying a candidate compound for increasing angiogenesis in a mammal, said method comprising:

(a) contacting Related Transcriptional Enhancer Factor-1 (RTEF-1) polypeptide with a candidate compound; and

(b) determining whether said candidate compound alters the biological activity of said RTEF-1 polypeptide, wherein a candidate compound that increases the biological activity of said RTEF-1 polypeptide is a candidate compound that may be useful for increasing angiogenesis.

63. The method of claim 61, wherein said candidate compound binds said RTEF-1 polypeptide.

64. A method for identifying a candidate compound for decreasing angiogenesis in a mammal, said method comprising:

(a) contacting Related Transcriptional Enhancer Factor-1 (RTEF-1) polypeptide with a candidate compound; and

(b) determining whether said candidate compound alters the biological activity of said RTEF-1 polypeptide, wherein a candidate compound that decreases the biological activity of said RTEF-1 polypeptide is a candidate compound that may be useful for decreasing angiogenesis.

65. The method of claim 63, wherein said candidate compound binds said RTEF-1 polypeptide.

66. The method of claim 62 or 64, wherein said RTEF-1 is human RTEF-1.

67. A method for identifying a candidate compound for increasing angiogenesis in a mammal, said method comprising testing the angiogenic activity of said candidate compound, wherein a compound that increases angiogenesis by at least 10% relative to a control is identified as a compound which may be useful for increasing angiogenesis.

68. A method for identifying a candidate compound for decreasing angiogenesis in a mammal, said method comprising testing the angiogenic activity of said candidate compound, wherein a compound that decreases angiogenesis by at least 10% relative to a control is identified as a compound which may be useful for decreasing angiogenesis.

69. A method of treating, preventing, or reducing hypoxia in a mammal at risk for or experiencing hypoxia comprising providing to said mammal a therapeutically effective amount of Related Transcriptional Enhancer Factor-1 (RTEF-1) polypeptide, wherein said RTEF-1 polypeptide has angiogenic activity and at least 80% sequence identity to the sequence of human RTEF-1 (Accession Number AAC50763), mouse RTEF-1 (Accession Number Q62296), or chick RTEF-1 (Accession Number P48984), and wherein said RTEF-1 polypeptide has angiogenic activity.

70. The method of claim 69, wherein said RTEF-1 is human RTEF-1.

71. The method of claim 69 further comprising providing a therapeutically effective amount of Hypoxia-Inducible Factor (HIF)-1α to said mammal.

72. The method of claim 69, wherein said RTEF-1 is provided to a cell, tissue, or organ of said mammal within or adjacent to an ischemic tissue.

73. The method of claim 69, wherein said RTEF-1 is provided by a cell, tissue, or organ of said mammal that has been modified to express said RTEF-1.

74. The method of claim 73, wherein said cell, tissue, or organ has at least 10% or more RTEF-1 polypeptide present, relative to a control cell, tissue, or organ.

75. A method of treating, preventing, or reducing hypoxia in a mammal at risk for or experiencing hypoxia comprising providing to said mammal a therapeutically effective amount of a nucleic acid molecule encoding Related Transcriptional Enhancer Factor-1 (RTEF-1) polypeptide, wherein said RTEF-1 polypeptide has angiogenic activity and at least 80% sequence identity to the sequence of human RTEF-1 (Accession Number AAC50763), mouse RTEF-1 (Accession Number Q62296), or chick RTEF-1 (Accession Number P48984), and wherein said RTEF-1 polypeptide has angiogenic activity.

76. The method of claim 75, wherein said RTEF-1 is human RTEF-1.

77. The method of claim 75 further comprising providing a therapeutically effective amount of a nucleic acid molecule encoding Hypoxia-Inducible Factor (HIF)-1α to said mammal.

78. The method of claim 75, wherein said nucleic acid molecule encoding RTEF-1 is provided to a cell, tissue, or organ of said mammal.

79. The method of claim 78, wherein said cell, tissue, or organ is within or adjacent to an ischemic tissue.

80. The method of claim 78, wherein said providing is *ex vivo* and said cell, tissue, or organ is administered to said mammal.

81. The method of claim 78, wherein said cell, tissue, or organ has at least 10% or more RTEF-1 polypeptide, present relative to a control cell, tissue, or organ.

82. The method of claim 78, wherein said cell, tissue, or organ is from an autologous source.

83. The method of claim 78, wherein said cell, tissue, or organ is from an allogeneic donor mammal.

84. The method of claim 78, wherein said cell is a myocyte, fibroblast, myoblast, endothelial cell, cardiomyocyte, cardioblast, or smooth muscle cell.

85. The method of claim 84, wherein said cell is an endothelial cell.

86. The method of claim 78, wherein said cell, tissue, or organ is, or is from, heart, liver, muscle, lung, pancreas, brain, skin, kidney, or eye.

87. The method of claim 75, wherein said nucleic acid molecule is an expression vector selected from the group consisting of a plasmid or a viral vector.

88. The method of claim 87, wherein said viral vector is selected from the group consisting of an adenovirus, retrovirus, adeno-associated virus vector, herpes simplex virus, SV40 vector, polyoma virus vector, papilloma virus vector, picarnovirus vector, and vaccinia virus vector.

89. The method of claim 75, wherein said nucleic acid molecule comprises a tissue-specific promoter that controls the expression of RTEF-1.

90. The method of claim 89, wherein said promoter is specific to endothelial cells, cardiomyocytes, skin cells, hepatocytes, myocytes, adipocytes, fibroblasts, or the tissue or cell type in which the RTEF-1 is to be provided.

91. The method of claim 69 or 75, wherein said mammal is diagnosed as having an ischemic condition.

92. The method of claim 91, wherein said ischemic condition is selected from the group consisting of cardiac infarction, chronic coronary ischemia, chronic lower limb ischemia, stroke, cerebral ischmemia, and peripheral vascular disease.

93. The method of claim 92, wherein said mammal is diagnosed as having myocardial ischemia.

94. The method of claim 69 or 75, wherein said mammal is diagnosed as having a myocardial infarct, unstable angina, cardiac hypertrophy, arrhythmia, cardiomyopathy, angina pectoris, atherosclerosis, arteriosclerosis, a complication of diabetes, restenosis, organ hypertrophy, organ hyperplasia, septic shock, inflammatory disease, or myocardial dysfunction.

95. The method of claim 69 or 75, wherein said providing is within three days before or after said mammal has a trauma or surgical procedure.

96. The method of claim 95, wherein said surgical procedure is selected from the group consisting of coronary bypass surgery, vascular surgery, percutaneous transluminal coronary angioplasty, percutaneous transluminal coronary intervention, and organ transplantation.

97. The method of claim 69, or 75, wherein said RTEF-1 increases VEGF, FGFR, or COX-2 levels in the target tissue of said mammal by at least 20% relative to an untreated control.

98. The method of claim 97, wherein said RTEF-1 increases VEGF, FGFR, or COX-2 levels in the target tissue of said mammal by at least 40% relative to an untreated control.

99. The method of claim 69, or 75, wherein said RTEF-1 induces collateral blood vessel formation, improves abnormal cardiac function, or increases contractility of heart muscle.

100. The method of claim 69, or 75, wherein said mammal is further provided with a second therapeutic regimen.

101. The method of claim 100, wherein said second therapeutic regimen is a therapeutic agent selected from the group consisting of nitrates, beta-blockers, calcium channel blockers, aspirin, nitroglycerin, chelation therapy, ethylenediaminetetracetic acid, anticoagulants, thrombolytic drugs, and tissue plasminogen activators.

102. The method of claim 100, wherein said second therapeutic regimen is surgery.

103. The method of claim 102, wherein said surgery is selected from the group consisting of coronary bypass surgery, vascular surgery, percutaneous transluminal coronary angioplasty, percutaneous transluminal coronary intervention, and organ transplantation.

104. The method of claim 100, wherein said second therapeutic regimen is exercise, reduction in smoking, reduction in alcohol intake, low sodium diet, low fat diet, low cholesterol diet, and stress management.

105. The method of claim 100, wherein said RTEF-1 polypeptide, or said nucleic acid encoding said RTEF-1 polypeptide, and said second therapeutic agent are provided within one hour of each other.

106. The method of claim 100, wherein said RTEF-1 polypeptide, or said nucleic acid encoding said RTEF-1 polypeptide, and said second therapeutic agent are provided simultaneously.

107. The method of claim 100, wherein said RTEF-1 and said second therapeutic agent are administered in the same pharmaceutical formulation.

108. A kit comprising:

(a) a vector encoding a Related Transcriptional Enhancer Factor-1 (RTEF-1) polypeptide in an amount sufficient to treat or reduce hypoxia; and

(b) instructions for delivery of said vector to a mammal or a tissue of said mammal for treating or reducing hypoxia.

109. The kit of claim 108, wherein said treatment or reduction of hypoxia comprises increasing angiogenesis in said mammal.

110. A kit comprising:

(a) a composition comprising a Related Transcriptional Enhancer Factor-1 (RTEF-1) polypeptide in an amount sufficient to treat or reduce hypoxia; and

(b) instructions for delivery of said composition to a mammal or a tissue of said mammal for treating or reducing hypoxia.

111. The kit of claim 110, wherein said treatment or reduction of hypoxia comprises increasing angiogenesis in said mammal.

112. A kit comprising:

(a) a composition that reduces the levels or activity of Related Transcriptional Enhancer Factor-1 (RTEF-1) in an amount sufficient to decrease angiogenesis; and

(b) instructions for delivery of said composition to a mammal or a tissue of said mammal for decreasing angiogenesis.

113. The kit of claim 112, wherein said composition comprises a peptide, a polypeptide, a synthetic organic molecule, a naturally occurring organic molecule, a nucleic acid molecule, an antibody, or an antigen binding fragment.

114. The kit of claim 113, wherein said nucleic acid molecule is a double stranded RNA (dsRNA) molecule for use in RNAi, or an antisense single stranded RNA (ssRNA) molecule.

115. A pharmaceutical composition comprising a compound that reduces the levels or activity of Related Transcriptional Enhancer Factor-1 (RTEF-1) and a pharmaceutically acceptable carrier.

116. The composition of claim 115 further comprising a second factor selected from a chemotherapy agent, a radiotherapy agent, a hormone ablation therapy agent, an anti-inflammatory agent, and a steroid.

117. The composition of claim 116 further comprising a compound that reduces the levels or activity of Hypoxia-Inducible Factor (HIF)-1α.

118. The composition of claim 115, wherein said compound is selected from a peptide, a polypeptide, a synthetic organic molecule, a naturally occurring organic molecule, a nucleic acid molecule, an antibody, and an antigen binding fragment.

119. The composition of claim 118, wherein said nucleic acid molecule is a double stranded RNA (dsRNA) moleucle for use in RNAi, or an antisense single stranded RNA (ssRNA) molecule.